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Review Article

Artonin E: A Short Review of its Chemistry, Sources, Anti-Cancer Activities and Other Pharmacological Properties

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ABSTRACT

In this short article, the chemistry, sources, anti-cancer and other medicinal properties of artonin E are reviewed for the first time. Sources of information cited on this prenylated flavonoid were from databases such as Google, Google Scholar, PubMed, Science Direct, J-Stage, Web of Science and PubChem. Artonin E or 5'-hydroxymorusin is a prenylated flavonoid from *Artocarpus* species (Moraceae). Its structure is that of a 3-isoprenyl 2',4',5'-trioxygenated flavone. Artonin E has been reported mostly in the root and bark of 12 *Artocarpus* species. The strong cytotoxic activities of artonin E are well-established and scientists from universities in Indonesia have been using artonin E as positive control when testing the cytotoxicity of compounds isolated from various plant species. The anti-cancer effects and mechanisms of artonin E have been reported in breast, lung, ovarian, colon and gastric cancer cells. Effects include apoptosis, anoikis, anti-proliferation, cell cycle arrest, inhibition of migration and invasion, and overcoming tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) resistance. Mechanisms include activation of caspases, up-regulation of apoptotic proteins and down-regulation of anti-apoptotic proteins. Artonin E is endowed with a wealth of other medicinal properties. A brief account on the medicinal properties and sources of other artonins is provided. Some prospects and further research on artonin E and other artonins are suggested.

Keywords: *Artocarpus*, 5'-Hydroxymorusin, Positive control, Apoptosis, Anoikis

Introduction

Prenylated flavonoids are a sub-class of flavonoids, which combine a flavonoid skeleton with a lipophilic prenyl side chain.[1,2] The side-chain can consist of prenyl, geranyl or lavandulyl moiety. To date, prenylated flavonoids have been identified in 37 of plant genera. More than 1000 prenylated flavonoids have been identified. Most of prenylated flavonoids are found in the families of Cannabaceae, Guttiferae, Leguminosae, Moraceae, Rutaceae and Umbelliferae.

Prenylation usually renders flavonoids with improved bioactivities. The prenyl side chain increases the lipophilicity of flavonoids, which enable them to have greater affinity to cell membranes.[1,3] Depending on the length of prenyl side-chain and flavonoid skeletons, prenylated flavonoids have diverse structures. Pharmacological properties of prenylated flavonoids include antioxidant, antibacterial, antiviral, antifungal, larvicidal, estrogenic, immuno-inhibitory, anti-cancer and anti-inflammatory.[1-3]

The genus *Artocarpus* consists of 50 species that are native to South and Southeast Asia, New Guinea, and the Pacific region.[4] *Artocarpus* species contain flavonoids that include 3-prenylflavones with a 2',4'-dioxygenated or 2',4',5'-trioxygenated pattern of ring B.[1] These 3-prenylflavones are rich in medicinal properties such as antimicrobial, anti-inflammatory and anticancer properties.

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Among the prenylated flavonoids is a group known as artonins. To date, 24 of such compounds (artonins A–Y) have been recorded.[5] Pharmacological properties of artonins include anti-plasmodial, anti-cancer and antibacterial activities.

In this article, the chemistry, sources, anti-cancer and other medicinal properties of artonin E from *Artocarpus* species are reviewed for the first time. A brief account on other artonins is included. Some prospects and future research on artonin E and other artonins are suggested.

Chemistry of Artonin E

Artonin E or 5'-hydroxymorusin from *Artocarpus* species (Moraceae) is a prenylated flavonoid with a molecular formula of $C_{25}H_{24}O_7$ and molecular weight of 436.5 g/mol.[6,7] The molecular structure of artonin E has three aromatic rings (A–C) with three OH groups at C2', C4' and C5' of ring B, and one OH group at C5 of ring A (Figure 1). There are two prenyl units, one isoprenoid substituent at C3 of oxygenated ring C and one forming a dimethylpyrane ring D at C7 and C8. The presence of a double bond between C2 and C3, and a carbonyl group at C4 are essential for the bioactivities of artonin E. Morusin has a similar molecular structure as artonin E except that it lacks the OH group at C5'. For this reason, artonin E is sometimes called 5'-hydroxymorusin.[6]

The structure of artonin E is a 3-isoprenyl 2',4',5'-trioxygenated flavone.[1,7] Other compounds with the same structural type are artoindonesianins L and U. Prenylated flavonoids also include 3-isoprenyl 2',4'-dioxygenated flavones such as artocarpin[8] and morusin.[9]

Sources of Artonin E

Artonin E was first isolated from the bark *Artocarpus altilis* (syn. *A. communis*)[10] (Figure 2). Subsequently, artonin E was reported in other *Artocarpus* species that include *A. chama*, *A. elasticus*, *A. gomezianus*, *A. kemando*, *A. lanceifolius*, *A. lowii*, *A. nobilis*, *A. rigida*, *A. rigidus* (syn. *A. rotunda*), *A. scortechinii* and *A. teysmannii* (Table 1). Plant part most reported are the root and bark, with no reports on the leaf.

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Antioxidant potentials of furanodihydrobenzoxanthones from *Artocarpus elasticus* and their protection against oxLDL induced injury in SH-SY5Y cells

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ABSTRACT

Exposure to reactive oxygen species (ROS) leads to the oxidation of low-density lipoproteins (LDL), converting them into oxidized ones (oxLDL), which are involved in the pathogenesis of Alzheimer's disease, suggesting a potential link between lipid dysregulation and neurodegenerative processes. Phenolic metabolites derived from *Artocarpus elasticus* root bark were found to possess significant antioxidant properties at three different radical scavenging assays, including 2,2-diphenyl-1-picrylhydrazyl (DPPH), oxygen radical absorbance capacity (ORAC), and thiobarbituric acid reactive substances (TBARS). Among them, furanodihydrobenzoxanthones (**1-3**) demonstrated notable protection against Cu^{2+} induced LDL oxidation, with IC_{50} values ranging from 0.9 to 2.9 μM in measurement of the malondialdehyde (MDA) production at TBARS and prolonged lag times (>180 min) in the generation of conjugated diene (CD). At a concentration of 10 μM, all three compounds (**1-3**) effectively protected against LDL oxidation as determined by relative electrophoretic mobility (REM). The most potent compound **1** defended human neuroblastoma SH-SY5Y cells from oxLDL-mediated dysfunction, including oxLDL-induced cytotoxicity, inhibited reactive oxygen species (ROS) formation, and enhancing mitochondrial membrane potential (ΔΨm). Individual components annotation in the ethylacetate extract was performed using LC-ESI-QTOF/MS, which serves as a chemotaxonomic marker for *A. elasticus* root barks.

1. Introduction

Oxidative stress leads to the formation of free radicals, also known as reactive oxygen species (ROS), which have been proposed as a potential trigger for various pathological conditions such as cancer, atherosclerosis, diabetes, and neurodegenerative disorders [1,2]. Endogenous antioxidants like superoxide dismutase and catalase can eliminate ROS, which are continuously produced in a living cell as byproducts of regular oxygen metabolism [3,4]. Accepting one electron, the oxygen molecule is converted to a superoxide anion-radical $O_2^{\cdot}$, with further reduction to hydrogen peroxide H_2O_2 [5]. Superoxide, either spontaneously or in the presence of transition metals, undergoes conversion into more potent forms such as the hydroxyl radical, leading to potential harm to numerous cellular components such as lipids, DNA, and proteins [6]. Thus, substances with antioxidant potential may have a possible effective therapeutic option in the treatment of ROS-induced disorders, due to its radical scavenging activity [7]. Antioxidant potential is usually tested by several types of radical sources, because each of them has its own benefits that we need to understand [8]. As an illustration, the 2, 2-diphenyl-1-picrylhydrazyl (DPPH) reaction favors single electron transfer (SET) and may even involve hydrophobic substances [9]. The best model of antioxidant reactions in the human body is the oxygen radical scavenging capacity (ORAC) assay, which employs peroxyl radicals [10]. They are quenched by the hydrogen atom transfer (HAT) mechanism. Among these is low-density lipoprotein (LDL) oxidation, in which LDL particles are damaged and converted into oxidative particles. This process leads to the formation of oxidative LDL species, which are involved in the development of atherosclerosis, which is also considered a risk factor for Alzheimer's disease (AD) [11]. Oxidation of LDL is induced by copper ions (Cu^{2+}), and state of LDL is then assessed *in vitro* by measuring the formation of lipid peroxidation products such as malondialdehyde (MDA), conjugated dienes (CD), and by monitoring changes in the physical properties of LDL particles using its relative electrophoretic mobility (REM) by gel electrophoresis and cell damage

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